

**Table S1:** References to accompany experimental support classifications in Figure 5. Genes listed produce the described phenotype if knocked out individually by setting the associated flux or fluxes to zero.

Gene(s)	Predicted Phenotype (Missing Metabolites)	Experimental Evidence and Categorization
<i>pabA</i> <i>folC,E,K</i>	5-Methyltetrahydrofolate	PabA is responsible for an early step from chorismate towards folate synthesis, and strains lacking it must be supplemented with p-aminobenzoic acid (Auxotroph) [1]. FolE, FolK, and FolC participate, in order, in later folate biosynthesis. <i>E. coli</i> lacks folate transporters, but precursor p-aminobenzoic acid can be transported from the media, so strains with defects in folate production prior to p-aminobenzoic acid can be supplemented. FolE and FolK catalytic steps occur before p-aminobenzoic acid (Likely Auxotrophs) [1]. FolC is essential because it participates after p-aminobenzoic acid (Other Agreement) [1].
<i>metF</i>	5-Methyltetrahydrofolate Methionine	5-methyltetrahydrofolate is a required cofactor in methionine synthesis, and MetF is required for transitions between this and other folate forms. Strains with <i>metF</i> mutations are methionine auxotrophs; however, it is unclear whether 5-methyltetrahydrofolate is required in the presence of methionine (Partial Agreement) [2].
<i>folA</i>	5-Methyltetrahydrofolate dTTP	Various folate-requiring products, such as methionine or thymine, do not restore growth in <i>folA</i> mutants. A number of other downstream metabolites are also required [3, 1]. An artifact of FBA allows this strain to produce methionine <i>in silico</i> (Partial Agreement) by cycling two forms of folate even though neither can be synthesized <i>de novo</i> .
<i>aroA,B,C</i>	5-Methyltetrahydrofolate Phenylalanine Tryptophan Tyrosine	<i>aroA</i> , <i>aroB</i> , and <i>aroC</i> gene products catalyze reactions in chorismate biosynthesis. Chorismate is required for folate cofactor and aromatic amino acid biosynthesis. These knockout strains are auxotrophs for the aromatic amino acids as well as the chorismate-derived precursors to folate and quinone biosynthesis (Auxotrophs) [4].
<i>guaA,B</i> <i>gmk</i>	5-Methyltetrahydrofolate dGTP FAD GTP	GuaA and GuaB participate in <i>de novo</i> guanine nucleotide biosynthesis. Both knockouts are purine auxotrophs. There are additional missing metabolites because folate and flavin synthesis rely on purines as precursors (Auxotrophs) [5]. Gmk is an essential kinase and loss of its function cannot be supplemented (Other Agreement) [6].
<i>gltA</i> <i>icd</i>	5-Methyltetrahydrofolate Arginine Glutamine Glutamate Proline Peptidoglycan Putrescine Spermidine	<i>gltA</i> and <i>icd</i> knockout strains require glutamate supplement in minimal media (Auxotrophs) [7, 8]. All other metabolites absent <i>in silico</i> depend on glutamate for biosynthesis (by pathway examination).

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<b>Gene(s)</b>	<b>Predicted Phenotype (Missing Metabolites)</b>	<b>Experimental Evidence and Categorization</b>
<i>panB, C, D</i> <i>coaD</i> <i>dfp</i>	Acetyl-CoA Coenzyme A Succinyl-CoA	<i>panB</i> , <i>panC</i> , and <i>panD</i> gene mutants are auxotrophic for pantothenate or beta-alanine, depending on the step being catalyzed. These intermediates contribute to Coenzyme A (CoA) biosynthesis (Auxotrophs) [9]. <i>Dfp</i> is also known as CoaBC, and along with <i>CoaD</i> it participates late in CoA biosynthesis (Other Agreement) [10, 11]. Strains which lack one of these gene functions slowly deplete Coenzyme A by dilution, ceasing division [12].
<i>cysC, E, H</i> , I, J, N	Acetyl-CoA Coenzyme A Cysteine Methionine Succinyl-CoA	<i>cysE</i> mutant strains require cysteine rather than other common ionic sulfur sources (Auxotroph) [13]. <i>cysC</i> and <i>cysH</i> gene products are required for growth on sulfate which is the sulfur source in our <i>in silico</i> M9 media (Auxotrophs) [13]. <i>cysI</i> , <i>cysJ</i> , and <i>cysN</i> gene products all participate in sulfur handling preceding cystine synthesis; mutants are rescued by cystine media supplement (Auxotrophs) [14]. Cystine is upstream of methionine synthesis and required for CoA synthesis.
<i>ilvC, D</i>	Acetyl-CoA Coenzyme A Isoleucine Leucine Succinyl-CoA Valine	<i>IlvC</i> and <i>IlvD</i> catalyze reactions preceding the valine and leucine pathways and analogous molecular steps in isoleucine synthesis. Precursors to these amino acids are also required in CoA synthesis. Mutants of <i>ilvD</i> and <i>ilvC</i> genes are auxotrophs for both isoleucine and valine (Auxotrophs) [15, 16].
<i>argG, H</i>	Arginine	<i>ArgG</i> and <i>ArgH</i> are responsible for the last two steps in arginine synthesis. <i>argG</i> mutant growth is limited by supplement of arginine, but grows slowly without it (Partial Agreement) [17]. <i>argH</i> mutants require arginine (Auxotroph) [18].
<i>argA, B, C, E</i>	Arginine Putrescine Spermidine	<i>argA</i> , <i>argB</i> , <i>argC</i> , and <i>argE</i> knockout strains are arginine auxotrophs. Putrescine can be produced either from ornithine or arginine precursors, so if arginine is supplemented the polyamines can be synthesized (Auxotrophs) [19, 18, 17].
<i>pgsA</i>	Cardiolipin Phosphatidylglycerol	Phosphatidylglycerophosphate synthase catalyzes the committed step in the biosynthesis of acidic phospholipids. This knockout strain experimentally lacks these two biomass constituents, and is only viable under some conditions: LB media 30°C (Other Agreement) [20].
<i>fabA, B, Z</i> <i>gpsA</i> <i>plsB, C</i>	Cardiolipin Phosphatidylethanolamine Phosphatidylglycerol Phosphatidylserine	Genes in this phenotype set participate in phospholipid and fatty acid biosynthesis. When <i>FabA</i> is inhibited the resulting growth defect is counteracted by media supplement of unsaturated fatty acids (Likely Auxotroph) [21]. <i>fabB</i> gene mutant is a fatty acid auxotroph (Auxotroph) [21]. <i>gpsA</i> and <i>plsB</i> mutant strains require glycerol or glycerol-3-phosphate to be supplied in the media for phospholipid synthesis (Auxotroph) [21]. There is no known supplement to rescue <i>fabZ</i> or <i>plsC</i> knockouts (Other Agreement). [21].

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**Table S1:** – continued from previous page

Gene(s)	Predicted Phenotype (Missing Metabolites)	Experimental Evidence and Categorization
<i>accA,B,C,D</i> <i>cdsA</i> <i>fabD,G,I</i>	Cardiolipin Lipopolysaccharide Phosphatidylethanolamine Phosphatidylglycerol Phosphatidylserine	Genes in this phenotype set participate in early phospholipid and fatty acid biosynthesis. <i>fabD</i> knockouts require saturated and unsaturated fatty acid supplements (Auxotroph) [21]. <i>accA</i> , <i>accB</i> , <i>accC</i> , <i>accD</i> , <i>fabG</i> , <i>fabI</i> , and <i>cdsA</i> genes are essential for growth (Other Agreement) [21].
<i>pyrG</i>	CTP dCTP	PyrG catalyzes the last step in <i>de novo</i> cytidine triphosphate biosynthesis. In <i>pyrG</i> mutants cytidine is required for growth, but the strain must contain an additional mutation to be viable due to toxic buildup of intermediates (Partial Agreement) [22].
<i>pyrB,C,D,E</i>	CTP dCTP dTTP UDPglucose UTP	<i>pyrB</i> , <i>pyrC</i> , <i>pyrD</i> , and <i>pyrE</i> gene products contribute to <i>de novo</i> biosynthesis of pyrimidines, and removal of any one of these genes results in purine requirement (Auxotrophs) [22].
<i>pyrH</i>	CTP dCTP Lipopolysaccharide Peptidoglycan UDPglucose UTP	PyrH is a uridine monophosphate kinase, and mutants of <i>pyrH</i> grow slowly without supplement (Partial Agreement) [22, 23]. Note that DTTP is still made because it can occur from precursors to UDP.
<i>thyA</i> <i>tmk</i>	dTTP	ThyA is responsible for the reaction dUMP to dTMP, the main pathway of <i>de novo</i> dTMP synthesis. Mutation creates auxotrophy (Auxotroph) [22]. Tmk phosphorelates dTMP to dTDP and knockout is lethal (Other Agreement) [24].
<i>ribA,B,C,D,E,F</i>	FAD	These genes participate in the pathway of flavin biosynthesis, or, in the case of RibF, the conversion between FAD and FMN. Flavin auxotrophs of the <i>rib</i> operon are mentioned non-specifically in literature as requiring very high riboflavin supplement because specific transport mechanism is lacking (Likely Auxotrophs) [25].
<i>hisA,B,C,D</i> <i>F,G,I</i>	Histidine	The genes in this operon were originally isolated as histidine auxotrophs (Auxotrophs) [26, 27, 28].
<i>ilvE</i>	Isoleucine	IlvE catalyzes the last step in isoleucine synthesis, and strains lacking it are isoleucine auxotrophs. Such mutants are also experimentally deficient in valine production, but do not absolutely require it (Auxotroph) [15, 29].
<i>leuA,B,C,D</i>	Leucine	This set of genes has products which function along the linear pathway towards leucine synthesis and were originally identified from leucine auxotrophs (Auxotrophs) [30].
<i>kdsA,B</i> <i>kdtA</i> <i>lpxA,B,C,D,K</i>	Lipopolysaccharide	Products of this gene set accomplish lipid A biosynthesis and LPS synthesis. Due to lipid A's role in anchoring LPS to the outer membrane it is essential and cannot be obtained from the media. <i>kdtA</i> , <i>kdsA</i> , <i>kdsB</i> , <i>lpxA</i> , <i>lpxC</i> , <i>lpxD</i> and <i>lpxK</i> knockouts are lethal (Other Agreement) [31, 32, 33, 34, 35]. <i>lpxB</i> mutants accumulate precursors but can survive (Partial Agreement) [31].

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<b>Gene(s)</b>	<b>Predicted Phenotype (Missing Metabolites)</b>	<b>Experimental Evidence and Categorization</b>
<i>glmS,U</i>	Lipopolysaccharide Peptidoglycan	<i>glmS</i> mutants are auxotrophs for glucosamine or N-acetylglucosamine (Auxotroph) [36]. GlnU has two functions and both are essential (Other Agreement) [37, 38, 31]
<i>psd</i>	Lipopolysaccharide Phosphatidylethanolamine	Converts phosphatidylserine (PS) to phosphatidylethanolamine (PE) lipid forms. PE is required and mutants of <i>psd</i> slowly stop growing (Other Agreement) [21, 39].
<i>pssA</i>	Lipopolysaccharide Phosphatidylethanolamine Phosphatidylserine	Synthesizes phosphatidylserine; mutation of <i>pssA</i> is lethal (Other Agreement) [39].
<i>lysA</i>	Lysine	LysA catalyzes the last step in lysine synthesis; mutants strains require lysine [40, 41].
<i>dapA,B,D,E</i>	Lysine Peptidoglycan	Synthesis pathway towards diaminopimelate which is either converted to lysine or use in peptidoglycan synthesis. These knockout strains require diaminopimelate supplement (Auxotrophs) [40].
<i>asd</i>	Lysine Methionine Peptidoglycan	Asd participates in lysine synthesis upstream of intermediate diaminopimelate, which either goes to lysine or peptidoglycan synthesis. A later intermediate in the pathway goes to methionine synthesis. Knockouts require diaminopimelic acid supplement, but because amino acid media was used the additional requirement for methionine was not specifically identified (Likely Auxotroph) [42, 43].
<i>metA,B</i>	Methionine	MetA and MetB participate in middle of methionine synthesis, and strains without them are auxotrophs for methionine or other pathway intermediates [44, 2, 45].
<i>nadA,B,C, nadE</i>	NAD NADH NADP NADPH	NadE is involved in <i>de novo</i> NAD <sup>+</sup> biosynthesis and salvage, catalyzing the final step of both pathways. Strains without <i>nadE</i> gene product function are unviable (Other Agreement) [46]. <i>nadA</i> , <i>nadB</i> , and <i>nadC</i> mutants are auxotrophs for pathway intermediates (Auxotrophs) [47, 46]
<i>nadK</i>	NADP NADPH	The <i>nadK</i> gene product is an essential NAD kinase (Other Agreement) [48].
<i>pheA</i>	Phenylalanine	<i>pheA</i> knockouts are phenelalanine auxotrophs (Auxotroph) [4].
<i>proC</i>	Proline	ProC is responsible for the final step in proline biosynthesis, strains without it are auxotrophic for proline (Auxotroph) [49].
<i>mraY, murA,B,C, D,E, F,G,I</i>	Peptidoglycan	Genes in this set catalyze steps in the peptidoglycan synthesis pathway. <i>murA</i> is essential and amber mutants die quickly in non-permissive conditions (Other Agreement) [50]. MurA–F are essential (Other Agreement) [51], as are Mray, MurI and MurG (Other Agreement) [52].

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Gene(s)	Predicted Phenotype (Missing Metabolites)	Experimental Evidence and Categorization
<i>metK</i>	Spermidine	The essentiality prediction appears consistent, but the predicted cause is not correct. In simulation, knockout prevents spermidine from being synthesized. However, spermidine is not a strictly essential metabolite [53]. Many other reactions (heme, quinone, biotin synthesis by examination of metabolic network) require the product of this reaction, and the gene is essential experimentally (Incorrect) [54].
<i>trpA,B,C,D,E</i>	Tryptophan	Gene products of <i>trpA</i> through <i>E</i> participate in the pathway of tryptophan synthesis, and their mutants are tryptophan auxotrophs (Auxotrophs) [55].
<i>tyrA</i>	Tyrosine	The <i>tyrA</i> knockout is a tyrosine auxotroph (Auxotroph) [4]
<i>serA,B,C</i>	All Biomass Metabolites, Severely impacted long-time: Acetyl-CoA Coenzyme A Cystine Methionine Phosphatidylserine Serine Succinyl-CoA	This set of gene knockouts are serine auxotrophs, but computationally exhibit total metabolism failure which is due to interference with cycling (Partial Agreement) [56].
<i>ppa</i> <i>prsA</i>	All Biomass Metabolites	Knockout of <i>ppa</i> or <i>prsA</i> genes computationally interferes with cycling in central metabolism, resulting in no function of the network in the short or long timescale. <i>ppa</i> codes for a pyrophosphatase which is essential, but the strains arrest slowly and not with an immediate cessation of all metabolism (Incorrect) [57, 50]. <i>prsA</i> (a.k.a. <i>prs</i> ) removal creates a requirement for a number of purine and pyrimidine end products, but does not inhibit all metabolic function (Incorrect) [58].
<i>pgk</i>	All Biomass Metabolites Decreased Moderately	Pgk functions in central metabolism and is essential. In contrast, the simulation can largely bypass its function with pathways that in reality do not compensate for loss of Pgk. (Incorrect) [59].
<i>atpB,C,E</i>	All Biomass Metabolites Decreased	<i>atpB</i> , <i>C</i> and, <i>E</i> are components of the membrane bound ATP synthase, and are among the few genes that produce an intermediate growth rate in FBA simulations based on the loss of efficiency in conversion of carbon substrate with the loss of the electron transport chain. Strains without these genes survive experimentally, albeit with slow growth (Other Agreement) [60].

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<b>Gene(s)</b>	<b>Predicted Phenotype (Missing Metabolites)</b>	<b>Experimental Evidence and Categorization</b>
<i>purH</i>	Histidine (Short Time) All (Steady State)	PurH performs the last steps in <i>de novo</i> purine synthesis, so blockage eventually leads to metabolism shutdown as purines are sequestered in biomass and cannot be synthesized as energy carriers. Immediate Histidine restriction is that purine synthesis consumes a side product of histidine synthesis which becomes a dead end when purine synthesis is blocked, which is partially consistent with experimental evidence [61]. <i>purH</i> is reported as a purine auxotroph (Partial Agreement) [6].
<i>purA,B,C,D,E</i> , All Biomass Metabolites <i>F,K,L,M</i> <i>adk</i>		Removal of the <i>pur</i> genes removes the ability to synthesize purines, without which metabolism eventually shuts down as energy carriers are depleted by inclusion of purines in cell mass. PurB is the next-to-last step in the pathway towards IMP, and also completes synthesis of AMP. All these <i>pur</i> gene knockouts in this set produce purine auxotrophs (Auxotrophs) [6]. The <i>adk</i> product is an AMP kinase and is essential (Other Agreement) [6].

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